REMARKS

Claims 6 and 7 are pending in this application. Claims 6 and 7 have been rejected and amended. No new matter has been added. Applicants are respectfully requesting reconsideration in view of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §112

Claim 7 has been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, it is suggested that the art supports unpredictability in the broadly drawn claims. The Examiner suggests that Matsumura et al. ((2004) *J. Cancer Res. Clin. Oncol.* 130:259-265) teach that the frequency of 1G/2G genotypes in gastric cancer patients was similar to controls; Lai et al. ((2005) *Gynecological Oncol.* 96:314-319) teach that the genetic polymorphisms of MMP-1 are not associated with risk of HSIL and SCC; Ju et al. ((2005) *Cancer Lett.* 217:191-196) teach that Koreans with specific polymorphisms in MMP-1 are neither more susceptible to develop cervical cancer nor more vulnerable for cancer progression; Babickova et al. ((2005) *Studia Pneumologica et Phthiseologica* 65:116-121) teach that the 1G/2G polymorphism of the MMP-1 gene is most probably not involved in the progression of tumors; Wenham et al. ((2003) *J. Soc. Gynec. Invest.* 10:381-387) teach that there is no relationship between the MMP-1 genotype and histological type, stage or tumor behavior; Benbow et al. ((2002) *J. Cell Biochem.* 86:307-319) teach that the VMM5 cell line which is 1G homozygous,

but invasive expresses high levels of MMP-1 constitutively and in the absence of the 2G allele these tumor cells may use alternative signal transduction pathways and cis-acting sequence to achieve high levels of MMP-1 expression; and Fang et al. ((2005) *Carcinogenesis* 26:481-486) teach that the MMP1G/5A haplotype significantly increases the risk of lymphatic metastasis compared with the 2G/6A haplotype. The Examiner further suggests that the analysis of the 1G/2G polymorphism was examined in 100 controls and several tumor cell lines and because the prior art establishes that cell lines are not appropriate means for examining associations with diseases. It is also suggested that the guidance provided in the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The Examiner suggests that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written. Applicants respectfully traverse this rejection.

The analyses carried out by Matsumura et al., Lai et al. and Ju et al., Babickova et al., Wenham et al., and Fang et al. were related to gastric cancer, cervical cancer, lung cancer, ovarian cancer, and non-small cell lung carcinoma. In contrast, Applicants have identified and enabled a correlation between invasiveness of melanoma tumor cells and the presence of the 1G/2G SNP of the MMP-1 promoter. Accordingly, in an earnest effort to clarify the present invention, Applicants have amended claim 7 to indicate that invasiveness of melanoma tumor cells is being assessed. Support for this amendment is found at page 10, lines 5-14, which states "for melanoma cells which produce MMP-1, the prognosis of the disease is correlated with tumor thickness

and depth of the invasion through dermal collagens (I and II), thereby indicating that invasiveness through these collagens serves as a valid prognostic marker. Accordingly detection of MMP-1 EBS-SNP, which is indicative of enhanced ability to degrade collagen types I, II, and III, in tumor cells of a patient serves as a useful prognostic marker in assessing the invasiveness of a particular tumor."

In so far as Benbow et al. disclose the VMM5 melanoma cell line which is 1G homozygous and expresses high levels of MMP-1 constitutively in the absence of the 2G allele, Applicants respectfully wish to point out that the instant method for assessing invasiveness of a melanoma tumor cell can be useful as one test in a panel of tests for assessing melanoma tumor cell invasiveness. With many diseases there are a plurality of genotypes which result in the disease phenotype. In this regard, the presence of the 1G/2G SNP of the MMP-1 promoter is one genotype resulting in invasive melanoma, whereas the 1G homozygous genotype of VMM5 cells is another genotype resulting in invasive melanoma.

Further, Applicants respectfully disagree with the Examiner's suggestion that cell lines are not indicative of associations with diseases. Applicants maintain that *in vitro* expression levels of proteins involved in tumor invasion are highly correlative of *in vivo* expression levels and invasiveness. For example, Stetler-Stevenson et al. ((1990) *J. Biol. Chem.* 265:13933-8; filed with Applicants' response dated February 15, 2005) teach a direct correlation between expression of human tissue inhibitor of metalloproteinases 1 and 2 in A2058 cells and expression of human tissue inhibitor of metalloproteinases 1 and

2 *in vivo*. Thus, the A2058 cell line is a highly representative model of *in vivo* tumor cells.

In view of Applicants' clarification of the instant method for assessing the invasiveness of a melanoma tumor cell and the direction provided in the instant specification as to the correlation between the 1G/2G genotype and invasiveness of melanoma tumor cells in an art-established tumor cell model, Applicants have clearly fulfilled the enablement requirement for making and using the invention without undue experimentation in accord with MPEP 2164.01(a). It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

Claims 6-7 have been rejected under U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. It is suggested that claims 6-7 are indefinite because it is unclear whether the claims are drawn to detecting SEQ ID NO:6 as indicative of the mutation or whether the claim is drawn to a SEQ ID NO:6 as the promoter sequence. It is suggested that the claim may be written to recite "comprising detecting in the matrix metalloproteinase-1 promoter sequence a 5'-AAGAT-3' to 5'-AAGGAT-3' Ets transcription factor binding site single nucleotide polymorphism wherein the promoter comprises SEQ ID NO:6 wherein the presence of the polymorphism is indicative of matrix metalloproteinase-1 overexpression in the cell." Applicants have made the appropriate amendment to the claims and respectfully request that this rejection be withdrawn.

Claim 7 is further rejected for reciting "increased invasiveness of the tumor cell" because it is unclear what the increase is compared to. Applicants respectfully disagree with

this rejection. However, in an earnest effort to clarify the instant method, Applicants have amended to the claim to indicate that the presence of the polymorphism in the melanoma tumor cell is indicative of matrix metalloproteinase-1 overexpression and invasiveness of the melanoma tumor cell. Page 10 (lines 5-14) of the specification teaches that overexpression of MMP-1 enhances a tumor's ability to degrade collagen types I, II, and III, wherein tumor thickness and depth is indicative of an invasive tumor. In light of this clarification, reconsideration and withdrawal of this rejection is respectfully requested.

II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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